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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,232	08/02/2003	Matthias Boldt	17835	2447

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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,232	BOLDT, MATTHIAS	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-5,14-19,21,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-13, 20, 22-27, and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election filed 25 September 2007 has been acknowledged and duly made of record.

Applicants elect: Group II, claims 6-13, 20, and 22-27. Claims 30-33 added in the previous communication also read on the elected invention.

A. Election.
Applicant confirms the previous election of Group II, claims 6-13, 20, and 22-27.

B. Specie Election For Group II.

Applicant elects enteral administration for examination on the merits.

C. Claims Readable On the Elected Species.

Claims 6-13, 20, 22, 30, and 32 read on the elected species.

Status of the Claims

Claims 1-33 are in the application. Claims 1-5; 15-19, 21, and 28-29 are pending but subject to restriction. Claims 6-13, 20, 22-27, and 30-33 are currently pending. II. Claim Amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived

by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-13, 20, 22-27 and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ajani et al. (USPN 5, 162,373) , Meglasson (USPN 5, 132, 324), Kornfelt et al. (USPN 5,652,216) and Kosbab (USPGPUB 2003/0108624 A1) in view of Yoshihara et al. (USPN 5,164,306).

Ajani et al. teach total parenteral nutrition formulations which include essential amino acids in combination with either arginine or ornithine, for use in detection of recurrent malignant disease in patients. Such formulations stimulate tumor-specific polyamine production to a greater

extent than non-tumor related polyamine production. Additionally, such formulations were found to specifically promote an increase in red block cell **putrescine** levels of tumor-bearing rats. Nontumor-bearing rats were not found to be similarly reactive to these formulations. Methods for making and administering these formulations as well as their use in preventing DFMO-induced toxicity are also disclosed (abstract only).

Ajani et al. teach **glutamine** has been shown to have a trophic effect on intestinal epithelium [...]. It has been demonstrated that the addition of glutamine(10-20 g/L) to a TPN solution restores gut epithelium (Op. Sit.). Specifically, recent studies have shown that oral glutamine protected the gut mucosa of rats receiving toxic doses of 5FU or methotrexate. Glutamine has also been shown to present transmucosal migration of bacteria into mesenteric lymph nodes compared to no such movement evident with the glutamine deficient formulas. Additionally, several investigators have shown that glutamine is an important energy substrate for tumors [...] suggests that glutamine should be administered orally to achieve regional protection without stimulating tumor growth. However, glutamine has been observed to have poor chemical stability in an aqueous solution. Specifically, the inclusion of glutamine in a TPN solution is limited by its breakdown to glutamic acid+NH.sub.3 (column 3, lines 35-56).

Ajani et al. further teach although the full advantages of the present invention are particularly exemplified through detection of a relative increase in putrescine measurement of all of the polyamines, including spermidine, spermine and putrescine is sufficient for most uses (column 5, lines 52-56).

Accordingly, Ajani et al. teach the L-glutamine. The instability of L-glutamine in solution has also been of concern to many tissue culture scientists, as glutamine is an essential

amino acid required by virtually all mammalian cells in culture regardless of type. Glutamine begins to break down chemically after only 2 days in storage at 21.degree. C. (room temperature), and only after 1 day stored at 35.degree. C. (room temperature) (Sigma Catalog, (1987), FIGS. 1 and 2, respectively, p. 1408). Glutamine stored at 4.degree. C. begins to degrade after 20 days in storage[…]. These factors led the Applicants to consider alternative formulations which would have the same "trophic" effect on mucosal epithelium as glutamine and which also remained chemically stable over extended periods of time (column 38, lines 5-19).

Ajani et al. teach amino acids for patients with malignant disease are desired which contains **alanine** as the non-essential amino acid of choice; the formula as outlined in Example III can be utilized. The same proportions of the essential amino acids (leucine, isoleucine, valine, phenylalanine, methionine, lysine, histidine, threonine, tryptophan and tyrosine) will be present; and the solution prepared in the same manner. Alanine will then be included at about a 1% by weight final concentration of the formula upon the addition of a glucose solution to the prepared stock. (column 29, lines 18-29).

Ajani et al. do not teach mono or dicreatine, trimethylglycerine, and guanidinopropionic acid GPA.

However, Yoshihara et al. teach a process for producing 5'-inosinic acid by culturing 5'-inosinic acid-producing bacteria in a medium containing inosine, and cane molasses, sucrose or glucose as the main carbon source and containing at least one of L-methylglycine, N,N-dimethylglycine, N,N,N –**trimethylglycine** and (2-hydroxyethyl)trimethylammonium in an amount effective to enhance the yield of 5'-inosinic acid, and harvesting the 5' inosinic acid produced (abstract only).

Specifically, Yoshihara et al. teach TMG is known as ***glycine betaine*** and contained in sugar beet, cotton seed, etc. in large quantities and, synthesized by reaction of chloroacetic acid with trimethylamine (column 4, line 60). Yoshihara et al. does not specifically teach trimethylglycine as indicated as a nutritional or supplemental ingredient within a formulation.

However, Kornfelt et al. teach a pharmaceutical preparation comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte, especially **an amino acid or dipeptide or a mixture thereof** and optionally an excipient (abstract only).

Accordingly, Kornfelt et al. teach a pharmaceutically acceptable ampholyte to be used in accordance with the invention may be selected from the group consisting of amino acids or derivations thereof such as glycine, ethylglycine (sarcosine), **trimethylglycine (betaine)**, alanine, .beta.-alanine, valine, leucine, nor-leucine, isoleucine, serine, threonine, aspartic acid, glutamic acid, hydroxyglutamic acid, lysine, hydroxylysine, omithine, arginine, histidine, methionine, asparagine and glutamine; dipeptides such as glycylglycine; pharmaceutically acceptable sulfonic acids or derivatives thereof such as taurine; creatinine, and ethylenediaminetetraacetic acid (EDTA) (column 2, lines 31 and 32).

The deficiencies of Kornfelt et al. in regard to art further suggesting TMG (betaine) as a nutritional ingredient are resolved by Kosbab

Kosbab teaches nutrient and therapeutic compositions for treatment and prevention of symptoms and disease conditions associated with microangiopathy and macroangiopathy and to methods using the compositions. In particular, the invention relates to compositions useful in the treatment of diabetic retinopathy and nephropathy, to compositions useful in the treatment of

other retinal disorders including macular degeneration and cataracts, to compositions useful in wound healing, to compositions useful for treatment and prevention of neuropathy, to compositions useful for treatment and prevention of cardiovascular disease and to compositions useful for the treatment and prevention of dental and periodontal disorders (abstract only).

Kosbab et al. teach dietary formulations and supplements in variable combinations comprising components such as L-alanine, betaine hydrochloride [0083], and creatine phosphate [which] is reported to have an anti-ischemic effect and to function as an anti-oxidant. It may also function to protect myocardial tissue from damage due to free radicals [0402].

The references *supra* do not specifically teach GPA in view of the various methods and compositions of the claimed invention.

However, Meglasson specifically teaches a method for treating or preventing certain metabolic disorders comprising the systemic administration of 3-guanidinopropionic acid (abstract only).

Meglasson teaches excess adiposity is an etiological factor in NIDDM and when extreme, represents a disease state in itself. 3-GPA decreases adiposity by decreasing the level of lipids stored in fat and liver tissue. The compound is therefore beneficial in the treatment of obesity alone or in concert with NIDDM. The effect of 3-GPA is selective for lipid-rich tissues (e.g., epididymal fat and fatty liver of ob/ob mice) while muscle mass is unaffected or only minimally affected (column 5, lines 28-36).

Further, Meglasson teaches by a pharmaceutical agent is meant that the 3-GPA compound or its salt, administered as claimed herein, is the only pharmaceutical agent

administered to the patient which has an effect on the metabolic disorders described herein (column 5, lines 43-47).

Still further Meglasson adequately addresses the inventive objective of claimed invention drawn to one of ordinary skill being inclined to administer 3-GPA compound or its salt to patients readily diagnosed with metabolic disorders *inter alia.*

The components which are disclosed in the claimed composition/formulation are well-known in the art for the same general therapeutic objective. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Thus, it would have been *prima facie* obvious to the skilled artisan at the time of invention to at once recognize a reasonable expectation of success via the combining and/or incorporating together the methods and compositions and explanations of Ajani et al., Kornfelt et al. Kosbab, Meglasson, and Yoshihara et al. The percentage concentrations in instant claim 20 are representative of therapeutic ranges taught in the art. Characterization optimization based on certain dietary requirements based on several factors specific to avoiding toxicity is well-known in the art.

The motivation to combine is shared between all the references cited above as they all essentially teach a compound, composition and/ or formulation comprising supplemental and dietary components which are well-known in the art as adjuvants in the effort toward therapeutic

efficacy. Ajani et al. teach embodiments drawn to specific combinations of some components as disclosed in instant claim 6. Kosbab, accordingly, teaches combination and supplemental therapy comprising components which overlap with Ajani et al., and which are both essentially drawn to the same therapeutic condition, i.e., metabolic disorders *inter alia.* The deficiencies in Ajani et al. and Kosbab are resolved by the remaining Kornfelt et al., Yoshihari et al. and Meglasson references which provides further motivation to combine. These latter references teach related subject matter and a similar inventive objective drawn to treatment of metabolic disorders as to further motivation to combine. More importantly, Meglasson teach other components drawn to the claimed invention which are known in the art to be combinable with the components of the references aforementioned.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information

about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB